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Potential Impact of Prescribing Metformin According to eGFR Rather Than Serum Creatinine

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Abstract

OBJECTIVE—Many societies recommend using estimated glomerular filtration rate (eGFR) rather than serum creatinine (sCr) to determine metformin eligibility. We examined the potential impact of these recommendations on metformin eligibility among U.S. adults.

RESEARCH DESIGN AND METHODS—Metformin eligibility was assessed among 3,902 adults with diabetes who participated in the 1999–2010 National Health and Nutrition Examination Surveys and reported routine access to health care, using conventional sCr thresholds (eligible if <1.4 mg/dL for women and <1.5 mg/dL for men) and eGFR categories: likely safe, ≥45 mL/min/1.73 m^2; contraindicated, <30 mL/min/1.73 m^2; and indeterminate, 30–44 mL/min/1.73 m^2). Different eGFR equations were used: four-variable MDRD, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine (CKD-EPIcr), and CKD-EPI cystatin C, as well as Cockcroft-Gault (CG) to estimate creatinine clearance (CrCl). Diabetes was defined by self-report or A1C ≥6.5% (48 mmol/mol). We used logistic regression to identify populations for

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whom metformin was likely safe adjusted for age, race/ethnicity, and sex. Results were weighted to the U.S. adult population.

RESULTS—Among adults with sCr above conventional cutoffs, MDRD eGFR ≥45 mL/min/1.73 m^2 was most common among men (adjusted odds ratio [aOR] 33.3 [95%CI 7.4–151.5] vs. women) and non-Hispanic Blacks (aOR vs. whites 14.8 [4.27–51.7]). No individuals with sCr below conventional cutoffs had an MDRD eGFR <30 mL/min/1.73 m^2. All estimating equations expanded the population of individuals for whom metformin is likely safe, ranging from 86,900 (CKD-EPIcr) to 834,800 (CG). All equations identified larger populations with eGFR 30–44mL/min/1.73 m^2, for whom metformin safety is indeterminate, ranging from 784,700 (CKD-EPIcr) to 1,636,000 (CG).

CONCLUSIONS—The use of eGFR or CrCl to determine metformin eligibility instead of sCr can expand the adult population with diabetes for whom metformin is likely safe, particularly among non-Hispanic blacks and men.

Healthy People 2020 goals include developing strategies for safe and effective glycemic control (1). One key strategy to attain this goal is to promote the use of metformin. Compared with other antidiabetes drugs, metformin is associated with decreased risk of cardiovascular events, progression of chronic kidney disease (CKD), and death (2,3). Also, it is well recognized that metformin has a better safety profile than other medications; in particular, it does not cause hypoglycemia, a common and potentially dangerous adverse effect of insulin secretagogues (4).

There is considerable reluctance, however, in using metformin among patients with CKD. Early pharmacokinetic studies demonstrated a prolonged half-life of metformin among individuals with severely impaired kidney function, placing them at heightened risk of lactic acidosis, a very rare (3.3–4.3 cases/100,000 patient-years) but serious metabolic complication that can occur in the setting of metformin accumulation (5). Thus, the U.S. Federal Drug Administration (FDA) has stated that metformin is contraindicated among individuals with kidney disease, “suggested by serum creatinine (sCr) ≥1.4 mg/dL for women and ≥1.5 mg/dL for men, or abnormal creatinine clearance (CrCl), which may result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia” (6).

As the benefits of metformin have become more widely appreciated, there has been an ongoing debate as to whether these sCr thresholds are too restrictive and whether the benefits of metformin outweigh potential harm among individuals with mild-to-moderate CKD. At the same time, evidence has accumulated that sCr leads to substantial misclassification in identifying individuals with CKD and that estimated glomerular filtration rate (eGFR) is a more accurate estimation of an individual’s kidney function. In 2012, the American Diabetes Association, Kidney Disease Improving Global Outcomes, European Association for the Study of Diabetes and U.K. National Institute for Health and Clinical Excellence all recommended metformin as a first-line agent for diabetes treatment among individuals with mild CKD, defined by eGFR ≥45 mL/min/1.73 m^2, and stated not to use metformin among individuals with severe CKD, defined by eGFR < 30 mL/min/1.73 m^2 (7–9). Because robust safety data are lacking for individuals with moderate CKD, defined by

an eGFR 30–44 mL/min/1.73 m^2, these societies recommended cautious use of metformin for individuals within this range, with frequent review and monitoring of kidney function.

Safely expanding metformin use among individuals with mild CKD may help improve outcomes among U.S. adults with diabetes. Our goals with this study were as follows: *1*) to determine prevalence and trends of metformin use among U.S. adults with diabetes from 1999 to 2010, *2*) to identify subpopulations of U.S. adults with diabetes for whom metformin is likely safe when implementing eGFR rather than conventional sCr thresholds, and *3*) to determine whether different GFR- or CrCl-estimating equations could have substantial impact on the number of individuals who would be considered safe candidates for metformin use.

RESEARCH DESIGN AND METHODS

Study Design

The National Health and Nutrition Examination Survey (NHANES) is conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics to examine trends in disease prevalence in cross-sectional representative samples of noninstitutionalized U.S. civilian residents (10). Survey data, released every 2 years, are collected during a standardized in-home interview and a physical examination/specimen collection at a mobile examination center.

Study Population

We examined data from 1999–2010 NHANES. The total number of adult (≥20 years) nonpregnant NHANES study participants with diabetes, defined by self-report or an A1C ≥6.5% (48 mmol/mol), was 4,324. We excluded individuals who had missing demographic data (n = 189) and those who did not report a routine site for health care (n = 241). These restrictions allowed the study population (final n = 3,902) to represent a group of individuals with a high likelihood of receiving diabetes treatment at a routine site of health care. All NHANES participants had given informed consent according to a protocol approved by an institutional review board (10).

Definitions

Metformin eligibility was defined using conventional sCr cutoffs: eligible if sCr < 1.4 mg/dL among women and < 1.5 mg/dL among men and ineligible if sCr ≥1.4 mg/dL among women and ≥1.5 mg/dL among men. Safe eGFR thresholds for metformin use were according to recent recommendations from American and European societies: likely safe if eGFR ≥45 mL/min/1.73 m^2, contraindicated if eGFR < 30 mL/min/1.73 m^2, and indeterminate if eGFR 30–44 mL/min/1.73 m^2. eGFR was calculated using different equations: *1*) four-variable MDRD study equation for calibrated sCr level (11), *2*) CKD-EPI creatinine (CKD-EPIcr) equation (12), and *3*) 2012 CKD-EPI cystatin C (CKD-EPIcys) equation (13). Creatinine clearance (CrCl) was estimated by the Cockcroft-Gault (CG) equation using actual body weight (14).

Measurements

Self-reported sociodemographics (age, sex, race/ethnicity, education, income), access to care (health insurance status, routine site for medical care), diagnoses (hypertension, diabetes mellitus), and type of antidiabetes medications (from prescription bottles provided by participants) were obtained during NHANES interviews. Blood pressure was measured during the mobile examination clinic visit; the mean of all measurements (up to four) was used. sCr was measured by the modified kinetic method of Jaffe, corrected for different analyzers and calibrated using isotope dilution mass spectrometry, with coefficients of variation ranging from 1.9 to 4.3 (15). Serum cystatin C was measured with the automated particle-enhanced nephelometric Dade Behring N Latex assay run on the Dade Behring Nephelometer II (16). The NHANES cystatin C assay had an intra-assay imprecision of 2.0–3.0% coefficient of variation and an interassay imprecision of 3.2–4.4% coefficient of variation. Random spot urine albumin and creatinine levels were measured using single frozen specimens from each participant. Urine albumin was measured using a solid-phase fluorescence immunoassay; urine creatinine was measured using the modified Jaffe kinetic method. Albuminuria and urine creatinine were corrected according to NHANES documentation to allow for comparison across all 12 years (17). Serum A1C was measured by high-performance liquid chromatography, with a maximum bias of ±0.35% and a precision that does not exceed an SD of 0.229.

Statistical Methods

Participant characteristics were compared by metformin eligibility by χ^2 and Wilcoxon rank-sum tests. Prevalence of diabetes medication use and trends over time were estimated overall and by NHANES survey year. Variance of proportions was estimated with Taylor series linearization. Multivariable logistic regression was used to identify populations eligible for metformin (i.e., eGFR ≥ 45 mL/min/1.73 m^2) among individuals with creatinine levels above conventional sCr cutoffs. Models were adjusted for age, sex, and race/ethnicity. Impact of different kidney function–estimating equations on the number of individuals who would be considered safe candidates for metformin use was calculated overall and by age, sex, and race/ethnicity. For these analyses, the study population was restricted to 1999–2002 adult NHANES participants with diabetes and self-reported routine access to care, as cystatin C was only measured during those years.

Sensitivity analyses with different study populations were performed to assess robustness of the results. First, we restricted the study population to individuals who self-reported diabetes only (vs. self-report and a laboratory-based definition of diabetes), increasing the likelihood that they would have an opportunity to be treated with antidiabetes medications (n = 3,214). Second, we restricted the study population to 2005–2010 NHANES participants to create a more contemporary cohort of patients eligible for metformin (n = 1,412). Third, we restricted the study population to individuals who self-reported diabetes between 2005 and 2010 NHANES (n = 1,171). All analyses were performed using the Survey Procedure commands in SAS, version 9.3 (SAS Institute, Cary, NC) using clusters, strata, and weights to obtain nationally representative population estimates.

RESULTS

Characteristics of the Study Population

Among NHANES adults with diabetes and routine access to care, 8.8% (study *N* = 342; estimated *N* = 1,328,400) were ineligible for metformin by conventional sCr thresholds and 83.8% (study *N* = 3,269, estimated *N* = 16,308,600) were eligible for metformin. A total of 291 individuals did not have creatinine data. Compared with individuals eligible for metformin, those ineligible were older and more likely to be non-Hispanic black or to have a yearly family income less than $45,000. There was a small but statistically significant higher prevalence of having health insurance among individuals not eligible for metformin. Prevalence of hypertension and macroalbuminuria was greater in those not eligible for metformin; BMI and glycemic control were similar in the two groups (Table 1).

Metformin Use Overall and by sCr Versus eGFR Categories

Across all 12 years, 66.4% of adults with diabetes were treated with a diabetes medication with a statistically significant increase over time: from 61.3% in 1999–2000 to 69.7% in 2009–2010 (P_{trend} = 0.03) (Fig. 1). Metformin use among persons with diabetes and a routine site for health care substantially increased over time, from 26.1 to 44.5% (P_{trend} < 0.001). Over the same period, concomitantly decreasing use of sulfonylureas and thiolidazinediones was noted, though these trends were nonsignificant.

The increase in metformin use between 1999 and 2010 was most pronounced among individuals with sCr ≤1.5 mg/dL and those with an MDRD eGFR ≥60 mL/min/1.73 m^2 (Supplementary Fig. 1). Between 2007 and 2010, an increase in metformin use among individuals with an eGFR 45–59 mL/min/1.73 m^2 and a decrease in metformin use among individuals with an eGFR 30–44 mL/min/1.73 m^2 were also noted (Supplementary Fig. 2).

Combining all 12 years of data, among individuals who were FDA eligible for metformin by conventional sCr thresholds, 40.7% (study *N* = 1,331, estimated *N* = 6,517,600) self-reported metformin use (Table 2). The majority of these individuals had an MDRD eGFR ≥45 mL/min/1.73 m^2. Among individuals who were FDA ineligible for metformin by conventional sCr thresholds, 15.5% (study *N* = 53, estimated *N* = 182,500) self-reported metformin use (Table 3). Among those who self-reported metformin use, 26.0% had an MDRD eGFR ≥45 mL/min/1.73 m^2 and 21.2% had an MDRD eGFR 30–44 mL/min/1.73 m^2. Comparable results were noted when the study population was restricted to *1*) adults with diabetes defined by self-report only, *2*) adult NHANES participants from 2005 to 2010, and *3*) adult NHANES participants from 2005 to 2010 with diabetes defined by self-report only (data not shown).

Individuals for Whom Metformin Is Likely Safe Despite Being FDA Ineligible

Among individuals ineligible for metformin using conventional sCr thresholds, 14.6% (study *N* = 50, estimated *N* = 148,700) had an MDRD eGFR ≥45 mL/min/1.73 m^2 and 50% (study *N* = 170; estimated *N* = 734,900) had an MDRD eGFR 30–44 mL/min/1.73 m^2, representing groups for whom metformin is likely safe and indeterminate, respectively. Only 35.7% (study *N* = 122, estimated *N* = 444,800) of individuals in eligible for metformin using

conventional thresholds had an MDRD eGFR < 30 mL/min/1.73 m^2, representing a population for whom metformin would be contraindicated by eGFR category (Table 4). Individuals for whom metformin would likely be safe because of an MDRD eGFR ≥45 mL/min/1.73 m^2 were predominantly men (adjusted odds ratio [aOR] vs. women 33.3 [95% CI 7.4–151.5]), < 60 years of age (aOR vs. ≥60 years 6.3 [1.26–31.7]), and non-Hispanic black (aORvs. whites 14.8 [4.27–51.7]) compared with individuals with an MDRD eGFR < 45 mL/min/1.73 m^2. There were no differences in BMI, glycemic control, or prevalence of hypertension across eGFR categories. Comparable results were noted when the study population was restricted to *1*) adults with diabetes defined by self-report only, *2*) adult NHANES participants from 2005–2010, and *3*) adult NHANES participants from 2005 to 2010 with diabetes defined by self-report only (data not shown).

Individuals for Whom Metformin May Not be Safe Despite Being FDA Eligible

Among individuals eligible for metformin using conventional sCr thresholds, no one had an MDRD eGFR < 30 mL/min/1.73 m^2. Over 98% (study N = 3,216, estimated N = 16,037,300) had an MDRD eGFR ≥45 mL/min/1.73 m^2, and 1.6% (study N = 53, estimated N = 271,300) had an MDRD eGFR 30–44 mL/min/1.73 m^2, representing populations for whom metformin is likely safe and indeterminate, respectively (Supplementary Table 1). Comparable results were noted when the study population was restricted to *1*) adults with diabetes defined by self-report only, *2*) adult NHANES participants from 2005–2010, and *3*) adult NHANES participants from 2005–2010 with diabetes defined by self-report only (data not shown).

Impact of Different GFR- and CrCl-Estimating Equations on Metformin Eligibility

All GFR- and CrCl-estimating equations expanded the pool of eligible metformin users compared with sCr. The magnitude of this change varied by equation, with national estimates ranging from 86,900 (CKD-EPIcr) to 834,800 (CG) (Supplementary Table 2). Consistent across all estimating equations, each subpopulation was predominantly male and non-Hispanic black (data not shown). For example, CKD-EPIcr expanded the national population of individuals eligible for metformin with an eGFR ≥45 mL/min/1.73 m^2 by 86,900 individuals, 100% of whom were male and 67% of whom were non-Hispanic black. Each estimating equation identified a much larger population of individuals for whom metformin safety was indeterminate (eGFR 30–44 mL/min/1.73 m^2). National estimates of this population ranged from 784,700 (CKD-EPIcr) to 1,636,000 (CG) (Supplementary Table 2).

CONCLUSIONS

This study has three key findings. First, although metformin use has increased in the past decade for treatment of the general population with type 2 diabetes, it remains underused among individuals with diabetes and mild kidney disease. Second, implementing eGFR or CrCl rather than sCr thresholds to determine individual eligibility for metformin could considerably expand the population eligible for its use, particularly among non- Hispanic blacks and men. Third, while various GFR- and CrCl-estimating equations identify different populations of individuals eligible/ineligible for metformin and all expand the population of

people with diabetes for whom metformin is likely safe, they also identify a large population of individuals for whom metformin safety remains unclear based on current U.S. recommendations.

The trend toward greater metformin use over the past decade is positive, as metformin remains the antidiabetes medication associated with the highest efficacy, the best cardiovascular profile, and the fewest unwanted side effects (2,4,18). Nationally representative data have recently demonstrated a decrease in diabetes complications over the same period (19). These improvements reflect advances in acute clinical care as well as chronic disease care and risk factor control. While speculative, it is possible that greater use of diabetes medications, and metformin in particular, for tighter glycemic control in the late 1990s and early 2000s may have contributed at least in part to these important public health gains.

Despite potential benefits, metformin remains underused among individuals with diabetes and mild kidney disease, who are at even greater risk of cardiovascular morbidity and mortality compared with the general population with diabetes (20). Creatinine thresholds are problematic for defining CKD. Creatinine production correlates with muscle mass and can underestimate or overestimate kidney function among individuals with muscle mass that differs from the population average. Estimates of GFR based on sCr, race, age, and sex are more clinically useful measures of kidney function, though they, too, must be cautiously interpreted among patients at anthropomorphic extremes. Nevertheless, these equations are recommended for medication dosing by several national and international nephrology societies. The Kidney Disease Outcomes Quality Initiative and Kidney Disease Improving Global Outcomes, for example, both recommend using metformin as a first-line agent among individuals with an eGFR of ≥45 mL/min/1.73 m^2 and to discontinue metformin definitively among individuals with an eGFR < 30 mL/min/1.73 m^2 (8,21). While our data do not allow us to ascertain clinician behavior, the sharp drop in metformin use among individuals with an eGFR < 45 mL/min/1.73 m^2 after 2007 compared with those with an eGFR ≥45 mL/min/1.73 m^2 allows us to speculate that the recommended eGFR thresholds are gaining importance in determining metformin eligibility.

Replacing sCr thresholds with eGFR thresholds could expand the pool of patients for whom metformin is likely safe without creating substantial safety concerns. Notably, 18% of individuals newly eligible for metformin in our study had an A1C >9% (75 mmol/mol). While uncontrolled diabetes is associated with more rapid renal function decline, studies have quoted rates of renal function decline ranging from −1.26 mL/min/1.73 m^2 per year to −3.24 mL/min/1.73 m^2 per year (22). Assuming at least yearly or more frequent monitoring of renal function among these patients, these rates of decline do not likely pose safety concerns and should not be impediments to metformin prescription. Thus, our study suggests that the number of individuals eligible for metformin in the U.S. can be expanded by at least 104,000, if using MDRD eGFR to calculate kidney function. This is a conservative estimate, as it does not take into account individuals who might be eligible for metformin with an MDRD eGFR 30–44 mL/min/1.73 m^2.

Approximately 50% of individuals with an sCr above the conventional threshold of metformin eligibility and 1.7% of individuals with an sCr below the conventional threshold had an MDRD eGFR between 30–44 mL/min/1.73 m^2. Individuals with diabetes and this level of kidney dysfunction are at higher risk of hypoglycemia, CKD progression, and mortality compared with individuals with less severe CKD, and may particularly benefit from metformin rather than a sulfonylurea or thiazolidinedione (23,24). Given the lack of robust data, current guidelines do not provide much guidance about metformin use in this population, though a few studies suggest its safety among individuals with a stable eGFR > 30 mL/min/1.73 m^2 (25). A randomized controlled trial is needed to clarify whether use of metformin in this subgroup would be safe and efficacious.

Importantly, the expanded pool of individuals for whom metformin is likely safe was predominantly male and non- Hispanic black. Prior European studies have documented that replacing creatinine thresholds with eGFR thresholds can minimize the number of males denied treatment with metformin (26,27). Our work builds upon these studies and identifies the potential impact of eGFR on metformin eligibility by race/ethnicity in addition to sex. Racial/ethnic disparities with respect to diabetes health outcomes are well recognized. Non-Hispanic black Americans with diabetes have worse glycemic control than their non-Hispanic white counterparts and have been demonstrated to shoulder a greater burden of diabetes complications, such as end-stage renal disease, retinopathy, neuropathy, and nontraumatic lower-extremity amputations (28–31). Paradoxically, recent studies have not shown differences in receipt of routine A1C testing, nephropathy screening, ormono-filament foot examination between non- Hispanic blacks and non-Hispanic whites when accounting for individual patient and facility variables (32). Non-Hispanic blacks generally have higher sCr than individuals of other race/ethnicities (33). Relying on eGFR rather than creatinine thresholds to determine metformin eligibility and safety may thus help bridge the gap between the aforementioned process and outcome measures (34).

The ideal method for estimating kidney function is an area of active research, as all kidney function–estimating formulas have inherent shortcomings compared with the gold standard of measured GFR using urinary or plasma clearance of exogenous filtration markers (35). CG estimates of CrCl are frequently used by pharmacists to determine medication dosing (36). However, CrCl is not readily available to clinicians who prescribe metformin. The National Kidney Disease Education Program reports that most laboratories use the four-variable MDRD and recommends it to determine medication safety (37). The newer CKD-EPIcr (12) generally has less bias than the four-variable MDRD and is slowly gaining traction among U.S. nephrologists and clinical laboratories (38); however, some studies suggest that it may perform less well than the four-variable MDRD equation when estimating GFR among individuals with type 2 diabetes (39). Recent data suggest that cystatin C–based equations may reclassify individuals into less severe stages of CKD and are more highly correlated with health outcomes than creatinine-based eGFR among patients with CKD (40). CKD-EPIcys has thus been recommended for confirmation of CKD status for elderly individuals in whom creatinine-based equations may not be accurate (41). Discrepancies in medication dosing using different kidney function–estimating equations have been well documented, particularly for elderly patients (42–44). However, to our knowledge, only one study has demonstrated the potential impact of these discrepancies on

health outcomes (45). In our study, while the CG equation expanded the number of individuals eligible for metformin the most, it also appeared to be the most conservative equation, reclassifying even more individuals to subpopulations for whom metformin is not safe or indeterminate. This is consistent with data demonstrating that CG underestimates GFR among patients with type 2 diabetes and overt diabetic nephropathy (46,47). Without hard outcomes, it is difficult to identify which kidney function–estimating equation is optimal to use to guide clinical decision making. Prospective studies should clarify the role of each equation for evaluation of safety and efficacy of medication dosing, including metformin, among CKD patients.

There are several limitations to this study, notably that NHANES is not a clinical database and includes community-dwelling individuals who do not seek medical care. However, we restricted our study population to participants who self-reported a routine site for health care and found similar results when restricting the study population to individuals who were aware of their diabetes. We could not ascertain the reasoning behind low levels of metformin use. Specifically, we could not determine whether this was due to patient nonadherence or lack of provider prescription, perhaps owing to nonrenal clinical conditions that contraindicate the use of metformin, such as liver disease. Additionally, NHANES relies on single measurements of eGFR and urinary albumin, leading to possible misclassification.

In summary, we demonstrate that metformin use may be expanded among adults with diabetes and mild CKD by focusing on eGFR rather than sCr thresholds for prescribing purposes, per recent national and international recommendations. In so doing, we may help mitigate racial/ethnic disparities in diabetes management and outcomes for non-Hispanic blacks. Additional research is needed to identify the best kidney function–estimating equation for optimal use and dosing of metformin at point of care. Lastly, it is important to identify the safety and efficacy of metformin among individuals with eGFR 30–44 mL/min/1.73 m^2, as this represents another potential avenue to further enhance diabetes care for adults at high risk of cardiovascular complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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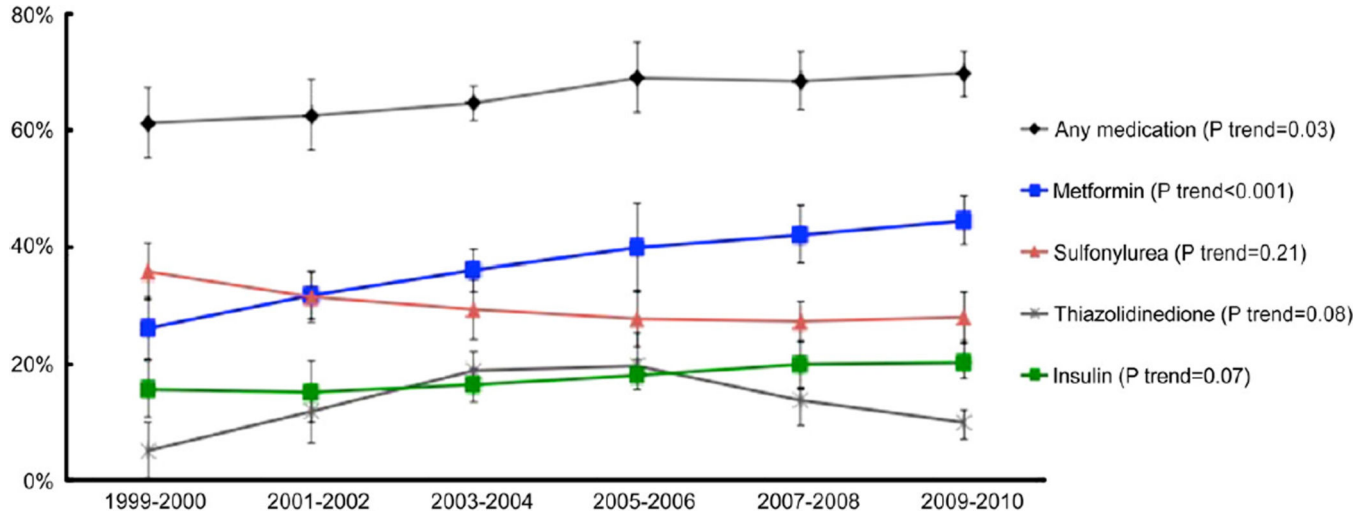

Figure 1.

Trends of diabetes medication use among individuals with diabetes and routine access to care: NHANES 1999–2010. Sample size = 3,902; sample weights used to produce U.S. national estimates. Diabetes is defined by self-report or A1C ≥6.5% (≥48 mmol/mol).

Table 1

Characteristics of adults with diabetes and routine access to care by conventional metformin eligibility status, NHANES 1999–2010

	FDA ineligible: sCr >1.4 mg/dL for women; >1.5 mg/dL for men		FDA eligible: sCr ≤1.4 mg/dL for women; ≤1.5 mg/dL for men		
	Of study *N* = 342	Of national estimate 1,328,400	Of study *N* = 3,269	Of national estimate 16,308,600	*P* (χ^2 or ANOVA)
Male sex	199 (58.2)	682,072	1,641 (50.2)	8,126,661	0.63
Age (years)					<0.001
20–39	3 (0.9)	13,763	206 (6.3)	1,518,262	
40–59	36 (10.5)	178,858	1,003 (30.7)	6,800,049	
60–69	107 (31.3)	388,365	1,041 (31.8)	4,071,965	
70+	196 (57.3)	747,369	1,019 (31.2)	3,918,311	
Race/ethnicity**					0.0007
White	142 (41.5)	835,991	1,294 (39.6)	10,394,879	
Non-Hispanic black	124 (36.3)	314,372	817 (25.0)	2,510,790	
Mexican American	58 (17.0)	69,714	766 (23.4)	1,273,053	
Yearly family income ($)					0.0001
<20,000	124 (40.4)	456,578	954 (32.4)	3,606,754	
20,000–44,999	122 (39.7)	477,204	1,051 (35.6)	5,202,546	
45,000–74,999	41 (13.4)	164,698	531 (18.0)	3,082,007	
>75,000	20 (6.5)	109,762	419 (14.2)	3,061,184	
Has health insurance	327 (95.61)	1,276,535	408 (12.6)	1,449,1185	0.01
More than high school education	137 (50.6)	632,030	1,431 (55.9)	9,133,441	0.007
Hypertension*	267 (78.8)	1,058,591	2,036 (67.7)	9,615,947	<0.001
Glycemic control: A1C					0.22
<7% (<53 mmol/mol)	200 (58.7)	817,351	1,735 (53.2)	8,890,542	
7–<8% (53–63 mmol/mol)	74 (21.7)	284,722	688 (21.1)	3,389,353	
8–<9% (64–74 mmol/mol)	33 (9.7)	104,007	330 (10.1)	1,565,172	
≥9% (>75 mmol/mol)	34 (10.0)	119,576	509 (15.6)	2,432,187	
BMI (kg/m^2), mean (SD)	32.6 (8.2)	33.02 (0.5)	32 (7.1)	32.65 (0.2)	0.51
MDRD eGFR (mL/min/1.73 m^2), mean (SD)	32.8 (12.6)	32.99 (0.7)	84.94 (25.4)	84.47 (0.5)	<0.001
Urine albumin-to-creatinine ratio (mg/g)					<0.001
≤30	103 (33.9)	439,836	2,187 (68.4)	11,556,713	
31–299	111 (36.5)	434,403	788 (24.7)	3,585,717	
300–1,000	33 (10.9)	128,431	151 (4.7)	572,633	

	FDA ineligible: sCr >1.4 mg/dL for women; >1.5 mg/dL for men		FDA eligible: sCr ≤1.4 mg/dL for women; ≤1.5 mg/dL for men		
	Of study *N* = 342	Of national estimate 1,328,400	Of study *N* = 3,269	Of national estimate 16,308,600	*P* (χ^2 or ANOVA)
>1,000	57 (18.8)	210,052	71 (2.2)	287,114	

Data are *n* (%) or *n* unless otherwise indicated. Sample weights used to produce U.S. national estimates. Diabetes is self-reported or A1C ≥6.5%. Entire sample size = 3,902; sCr data are missing from 291 study participants.

* Hypertension defined by average blood pressure >140/90 mm Hg or self-reported antihypertensive medication use.

** "Other" not shown owing to small sample size but included in all analyses.

Table 2

Metformin self-report among adults with diabetes and routine access to care who are FDA eligible for metformin by conventional sCr thresholds by eGFR category, NHANES 1999–2010

	FDA eligible for metformin (sCr <1.4 mg/dL for women; <1.5 mg/dL for men)			
		Metformin self-report		
	Overall study *N*	Study *N*	%	National estimate (*n*)
All	3,269	1,331	40.7	6,517,600
MDRD eGFR <30 mL/min/1.73 m^2	0	0	0	0
MDRD eGFR 30–44 mL/min/1.73 m^2	53	18	34.0	85,400
MDRD eGFR ≥45 mL/min/1.73 m^2	3,216	1,313	40.8	6,432,200

Weights used to produce U.S. national estimates.

Table 3

Metformin self-report among adults with diabetes and routine access to care who are FDA ineligible for metformin by conventional sCr thresholds by eGFR category, NHANES 1999–2010

	FDA ineligible for metformin (serum creatinine ≥1.4 mg/dL for women; ≥1.5 mg/dL for men)			
		Metformin self-report		
	Overall study *N*	Study *N*	%	National estimate (*n*)
All	342	53	15.5	182,500
MDRD eGFR <30 mL/min/1.73 m^2	122	4	3.3	5,800
MDRD eGFR 30–44 mL/min/1.73 m^2	170	36	21.2	120,800
MDRD eGFR ≥45 mL/min/1.73 m^2	50	13	26.0	55,800

Weights used to produce U.S. national estimates.

Table 4

Characteristics of adults with diabetes and routine access to care who are FDA ineligible for metformin, NHANES 1999–2010

	Metformin is contraindicated: MDRD eGFR <30 mL/min/1.73 m^2		**Indeterminant: MDRD eGFR 30–44 mL/min/1.73 m^2**		**Metformin is likely safe: MDRD eGFR ≥45 mL/min/1.73 m^2**		
	Of study *N* = 122	**Of national estimate *N* = 444,800**	**Of study *N* = 170**	**Of national estimate *N* = 734,900**	**Of study *N* = 50**	**Of national estimate *N* = 148,700**	***P* (x^2 or ANOVA)***
Male sex	54 (44.3)	158,300	97 (57.1)	384,533	48 (96.0)	139,200	<0.001
Age (years)							0.00
20–39	1 (0.8)	5,700	0 (0.0)	0	2 (4.0)	8,100	
40–59	18 (14.8)	77,300	13 (7.7)	63,300	5 (10.0)	38,200	
60–69	40 (32.8)	117,600	44 (25.9)	206,400	23 (46.0)	64,400	
70+	63 (51.6)	244,200	113 (66.5)	465,200	20 (40.0)	38,000	
Race/ethnicity**							<0.001
White	41 (33.6)	257,300	96 (56.5)	546,400	5 (10.0)	32,400	
Non-Hispanic black	40 (32.8)	103,100	44 (25.9)	125,900	40 (80.0)	86,400	
Hispanic	33 (27.1)	39,400	22 (12.9)	35,200	3 (6.0)	1,900	
Yearly family income ($)					2 (4.0)		0.20
<20,000	38 (35.2)	117,700	72 (47.1)	300,000	14 (30.4)	39,200	
20,000–44,999	51 (47.2)	214,000	51 (33.3)	220,000	20 (43.5)	43,300	
45,000–74,999	14 (13.0)	48,000	19 (12.4)	86,500	8 (17.4)	30,100	
≥75,000	5 (4.6)	23,000	11 (7.2)	56,100	4 (8.7)	30,700	
Has health insurance	118 (96.7)	438,600	163 (95.9)	701,500	46 (92.0)	136,500	0.37
Greater than high school education	49 (49.5)	208,200	66 (50.0)	334,600	22 (55.0)	89,300	0.82
Hypertension*	100 (82.6)	365,100	127 (75.2)	570,300	40 (81.6)	123,200	0.27
Glycemic control: A1C							0.32
<7% (<53 mmol/mol)	74 (61.2)	295,200	99 (58.2)	444,200	27 (54.0)	78,000	
7–<8% (53–63 mmol/mol)	27 (22.3)	83,700	40 (23.5)	183,300	7 (14.0)	18,000	
8–<9% (64–74 mmol/mol)	20 (8.3)	28,000	16 (9.4)	65,300	7 (14.0)	10,700	
≥9% (>75 mmol/mol)	10 (8.3)	35,300	15 (8.8)	42,400	9 (18.0)	41,900	
BMI (kg/m^2), mean (SD)	31.7 (6.5)	—	33.3 (9.1)	—	32.4 (8.9)	—	0.31

	Metformin is contraindicated: MDRD eGFR <30 mL/min/1.73 m^2		Indeterminant: MDRD eGFR 30–44 mL/min/1.73 m^2		Metformin is likely safe: MDRD eGFR ≥45 mL/min/1.73 m^2		
	Of study *N* = 122	Of national estimate *N* = 444,800	Of study *N* = 170	Of national estimate *N* = 734,900	Of study *N* = 50	Of national estimate *N* = 148,700	*P* (x^2 or ANOVA)***
Urine albumin-to-creatinine ratio (mg/g)							<0.001
≤30	18 (18.2)	63,500	66 (42.0)	312,700	19 (39.6)	63,700	
31–299	32 (32.2)	151,800	60 (38.3)	229,300	19 (39.6)	53,300	
300–1,000	14 (14.1)	49,100	13 (8.3)	65,600	6 (12.5)	13,600	
>1,000	35 (35.4)	117,300	18 (11.5)	78,800	4 (8.3)	14,000	

Data are *n* (%) or *n* unless otherwise indicated. FDA ineligible for metformin: sCr ≥1.4 mg/dL for women and ≥1.5 mg/dL for men. Sample size = 342; weights used to produce U.S. national estimates. Diabetes is self-reported or A1C >6.5%.

*** *P* values refer to differences among actual study participants—not national estimates.

** "Other" not shown owing to small sample size but included in all analyses.

* Hypertension defined by average blood pressure >140/90 mm Hg or self-reported antihypertensive use.

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